Antihypertensive Therapy

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Effective antihypertensive drug therapy began with the ganglion-blocking agents, followed by reserpine and hydralazine. Later advances included the benzothiadiazine saluretic agents and more recently compounds which specifically inhibit the sympathetic nervous system, such as guanethidine, alpha-methyldopa, and certain amine oxidase inhibitors. Among the antihypertensive drugs, molecular modifications seem to have yielded the greatest clinical benefits in the period immediately following the discovery of an agent with a new type of action. Further improvements have been limited because of inability to circumvent objectionable side effects which were indissolubly linked with the mode of antihypertensive action of a given class of compounds.

It is remarkable that effective antihypertensive agents have been developed entirely during the past 15 years. The thread which ties together this period of therapeutic progress has been based on a continuous interchange of information between the clinic and the chemical laboratory, in which specific therapeutic needs have motivated the direction of chemical development. This paper discusses the manner in which new compounds lead not only to therapeutic advances but also to fresh problems. It also indicates how molecular modifications have been used sometimes successfully, sometimes fruitlessly, to meet the continuing demands of the clinician.

Ganglion-Blocking Agents

The main path of development of antihypertensive agents began with the observation that tetraethylammonium chloride inhibited the transmission of nerve impulses through sympathetic ganglia in both animals and man and transiently lowered blood pressure in hypertensive patients (*12*). Paton and Zaimis (*15*) then proceeded to investigate a series of quaternary ammonium salts in which varying numbers of methylene groups were interposed between

two trimethylammonium cationic heads. The higher members of the series, such as decamethonium, were found to have a curare-like action—that is, they produced paralysis of voluntary muscle. The compounds with fewer methylene groups produced ganglion-blocking action; hexamethonium appeared to be the most effective and was found to be a potent antihypertensive agent. It represented the first clinically practical drug treatment for severe hypertension (*6, 16*). The reversals of malignant hypertension to a more benign phase of the disease were so dramatic that they revolutionized the methods of treating hypertension which, until that time, had been dominated by surgical sympathectomy and low-salt diets.

There were, however, many undesirable features related to hexamethonium treatment. The drug was not very effective or predictable in its action when given by mouth, unless the doses were pushed to high levels and, at these high doses, severe side effects could occur. Paralysis of the bowel was a particularly dangerous reaction when large doses had been given orally, since a large amount of the drug remained in the intestinal tract, prolonging and aggravating the toxic effect. Because of poor absorption, the drug was given by injection in most cases, in the same manner as insulin in a diabetic. An unusual toxic reaction associated with hexamethonium was pneumonic infiltration of the lung, which was not seen with the blocking agents developed later.

Because of potentially severe toxicity and the need for parenteral injections, pharmaceutical research was directed toward developing ganglion-blocking agents which would be less toxic and could be effectively administered orally. Such a drug, another diquaternary ammonium salt, was soon discovered and was given the name of pentolinium tartrate (*7, 20*). There was no doubt that pentolinium, or Ansolysen, represented a considerable improvement over hexamethonium. It was more potent, much more effective by mouth, and somewhat longer acting, and caused no pneumonitis and far less paralysis of the bowel. It quickly replaced hexamethonium as the treatment of choice in severe hypertension.

Pentolinium, however, had certain disadvantages which made it impractical for the treatment of mild or moderate hypertension. The disturbing side effects associated with blockade of the sympathetic and parasympathetic nervous system were still present: constipation, dry mouth, impotence, chilling in a cold environment, and blockade of the reflex adjustment of blood pressure which normally occurs when the patient assumes the erect position. Occasionally, the postural hypotension was so severe that there was insufficient blood flow to the brain and the patient fainted.

Another feature of all ganglion-blocking drugs was that the blood pressure fluctuated considerably from very low to high values. Despite careful adjustment of the dose, this fluctuation could not be done away with entirely. In the attempt to prevent the peaks of pressure the doses were elevated so that the patient at another time might be unable to stand erect because of postural hypotension.

Quaternary ammonium bases are poorly absorbed from the gastrointestinal tract. In the case of hexamethonium and pentolinium less than 10% of the ingested dose is actually absorbed. Further development of effective ganglion-blocking agents, therefore, was directed toward improving absorption. It was hoped that the fluctuations in blood pressure and the severity of the side effects

associated with pentolinium would be overcome if the blocking agent was completely absorbed.

This reasoning led to the development of mecamylamine by Stone and his associates (*19*). Mecamylamine is not a quaternary base but rather a secondary amine which permits complete absorption from the gastrointestinal tract. This modification unfortunately did not strikingly improve therapeutic effectiveness (*8*). Clinical trials soon showed that the fluctuating blood pressure response associated with the ganglion-blocking agents was not due primarily to variable absorption.

Saluretic Agents

This clinical experience with mecamylamine made it clear that the cause of the variable responsiveness to the ganglion-blocking drugs was not poor absorption but rather changes in the responsiveness of the patient's blood pressure to ganglionic blockade. A most important factor was the state of hydration, or amount of salt and water in the body (*5*). When patients became edematous they required larger doses of blocking agents to lower their blood pressures, and the blood pressure was more difficult to control even with the larger dose. Thus, accumulation of salt and water, leading to expansion of extracellular fluid volume, produced increased resistance to the antihypertensive effects of ganglion-blocking drugs. Contrariwise, mercurial diuretics or salt-depleting diets made patients more responsive to these blocking agents. Furthermore, salt-depleting procedures lowered blood pressure moderately in hypertensive patients even in the absence of other drugs. These observations led to the next major development in antihypertensive therapy: the discovery of practical agents for inducing and maintaining a state of moderate salt depletion in hypertensive patients.

This development came about through a series of molecular modifications which began with the basic observation that certain sulfonamide drugs inhibit the enzyme carbonic anhydrase. The diuretic acetazolamide was one practical result of such investigations.

In a systemic program of molecular modification of the benzenedisulfonamides, Novello and Sprague, in collaboration with the pharmacologists Baer and Beyer, observed an unexpected high order of diuretic activity in such compounds as benzene-1,3-disulfonamide (*17*). Their investigation led eventually to cyclic compounds, of which chlorothiazide appeared to be one of the most active. Chlorothiazide was only a weak carbonic anhydrase inhibitor and its mode of action was not the same as that of either the mercurials or acetazolamide. However, chlorothiazide was well absorbed after oral administration and was effective in causing sodium excretion in hypertensive patients. The initial antihypertensive effect of the drug appeared to be accompanied by a reduction of plasma volume associated with the saluretic effect (*5*).

Certain side reactions are associated with long-term treatment with chlorothiazide. The most common side effect is a reduction in serum potassium concentration. There is also an elevation in serum uric acid concentration, occasionally with precipitation of acute attacks of gout. In rare instances, hyperglycemia and diabetes mellitus have occurred. Numerous molecular modifications have since been made, with the hope of producing a compound

that would retain the sodium diuretic effect but not induce potassium loss or uric acid retention. Despite considerable work, these efforts have not succeeded in developing an agent with significantly improved clinical usefulness.

Hydrogenation of the chlorothiazide molecule led to hydrochlorothiazide, which permitted the dose to be reduced tenfold, but the only practical advantage was that the patient took less drug. This, and various other modifications of the basic compound, led to insignificant changes in electrolyte excretion ratios which were of little practical value clinically.

A compound of somewhat related structure, chlorthalidone, is of interest because of its long duration of action and considerable potency (*13*). A convenient single-dose-per-day schedule is sufficient to induce and maintain an adequate natriuresis. At times, some of our patients seem to become tolerant to chlorothiazide and transferring their medication to chlorthalidone again invokes a saluretic effect. However, chlorthalidone induces the same hypokalemia and hyperuricemia that has been so frequently observed during long-term treatment with the benzothiadiazines.

An interesting new development has been the discovery that certain pteridine compounds promote sodium excretion and, at the same time, potassium retention. Clinical studies in hypertensive patients carried out with triamterene indicated that the drug was not in itself sufficiently potent as a natriuretic agent in hypertensive patients to be clinically useful (*10*). When combined with half-strength doses of hydrochlorothiazide, however, its natriuretic effect was comparable to that obtained with full doses of hydrochlorothiazide but without significant urinary loss of potassium or reduction in serum potassium concentration. Thus, triamterene may represent a beginning in the development of new compounds with more specific natriuretic properties.

Adrenergic Blocking Drugs

With the combined use of chlorothiazine and ganglion-blocking agents, the chemotherapeutic method for controlling severe hypertension became firmly established. The disturbing side effects produced by the ganglion-blocking agents, however, remained a definite nuisance. Patients complained not only of side reactions produced by sympathetic blockade, such as weakness and faintness in the erect position due to postural hypotension, but also of parasympathetic blocking effects which included constipation, dryness of the mouth, failure of visual accommodation, difficulty in emptying the urinary bladder, and impotence. Therefore, a search was made for compounds which would block the sympathetic system selectively, leaving parasympathetic functions undisturbed.

As a result of this search, a number of new compounds with interesting properties have been developed. These include bretylium tosylate (*2*), guanethidine (*14*), methyldopa [3-(3,4-dihydroxyphenyl)alanine] (*18*), and pargyline (*11*). All these compounds produce a more selective inhibition of the sympathetic nervous system, although each differs somewhat one from the other, in both primary mode of action and clinical effects. Of these compounds, guanethidine has received the most extensive therapeutic trial and clinical acceptance.

Guanethidine was the outgrowth of certain pharmacological observations

made by Maxwell, Plummer, and coworkers, on compound SU-4029 (*14*). SU-4029 antagonized the pressor effects of amphetamine and ephedrine, blocked the carotid occlusion pressor reflex, and lowered blood pressure in neurogenic and renal hypertensive dogs. The duration of action was remarkably prolonged over a period of several weeks. SU-4029 produced disturbing side reactions in clinical trials but guanethidine did not, thus providing another example of successful molecular modification.

Guanethidine lowers blood pressure in hypertensive patients by reducing both cardiac output and total peripheral resistance (*4*). There also is some redistribution of blood flow, so that less of the cardiac output is distributed to the intestines and liver. When guanethidine is given to patients intravenously, there is a transient period of elevation of cardiac output and rate and blood pressure, suggesting that catecholamines have been released (*4*). The duration of action of the drug in man appears to be about one week, so that doses taken daily tend to be cumulative over that period (*9*). As with the ganglion-blocking drugs, the effective hypotensive dose varies widely from one patient to another, and the saluretic agents enhance the antihypertensive effects of guanethidine. The side effects are considerably less than with the ganglion-blocking agents and the blood pressure seems to fluctuate to a lesser degree.

The newer antihypertensive agents, of which guanethidine is one example, represent an outgrowth of current concepts of catecholamine metabolism. It is now believed that norepinephrine is stored in the form of granules in the sympathetic nerve endings (*3*). Under adequate stimulation, the norepinephrine is released to constrict the smooth muscle of blood vessels or increase the force of contraction of the heart, thereby raising blood pressure. Certain pressor amines such as tyramine and ephedrine are believed to act in this fashion by releasing the norepinephrine stored in the nerve endings. Reserpine, an antihypertensive agent that we have not yet discussed, produces depletion of the norepinephrine stores (*3*). Guanethidine may also act in somewhat the same fashion, although the clinical effects of guanethidine and reserpine are different. Although guanethidine may produce some release of catecholamines on intravenous administration, the exact mechanism of action of this drug has not been clarified, except that it produces some sort of a peripheral block of the sympathetic nervous system (*14*).

Methyldopa was synthesized for the purpose of inhibiting the decarboxylation of dopa to dopamine, which is believed to be the precursor of norepinephrine (*18*). Thus methyldopa should prevent the formation of catecholamine stores. It seems probable that the mode of antihypertensive action of methyldopa is more complex than simple inhibition of norepinephrine synthesis. Clinically, the drug lowers blood pressure with less prominent orthostatic hypotension than guanethidine. However, some patients seem to be resistant to the drug and it is not generally dependable in reducing blood pressure as is guanethidine (Figure 1).

It has been known for some time that monoamine oxidase inhibitors will lower blood pressure in hypertensive patients and produce orthostatic hypotension. Theoretically, by preventing the metabolic degradation of norepinephrine, such compounds should raise blood pressure by increasing catecholamine stores. However, these enzyme inhibitors also have other actions, including a ganglion-blocking effect. Early trials with monoamine oxidase inhibi-

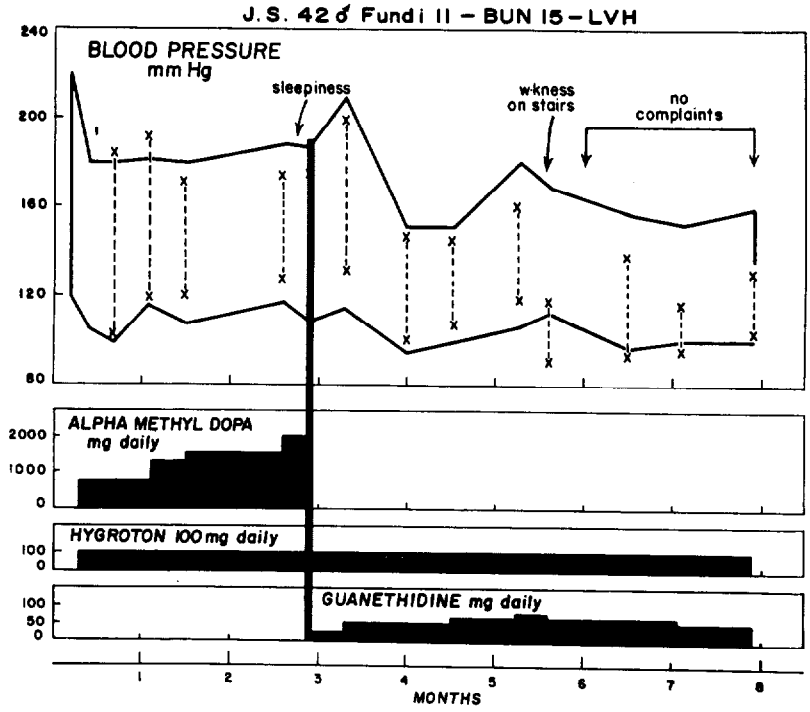

Figure 1. Effect of alpha-methyldopa and chlorthalidone (Hygroton) compared to guanethidine plus chlorthalidone in patient with hypertension resistant to treatment

Vertical dashed lines indicate blood pressure readings taken while patient was standing in erect position. Alpha-methyl-dopa did not control blood pressure in this patient, but did not produce postural hypotension seen with guanethidine

tors in the treatment of hypertension were disappointing because of the development of toxic reactions associated with the hydrazine group. More recently, pargyline, which does not contain a hydrazine, has been shown to exert monoamine oxidase activity and also to be a potent antihypertensive drug (*11*). Clinical experience confirms the active antihypertensive effect, including orthostatic hypotension. Final evaluation of pargyline and alpha-methyldopa as antihypertensive agents must await more extensive clinical trials.

Other Antihypertensive Agents and Combinations

This survey would not be complete without mentioning the Veratrum alkaloids (whose use is limited because of their emetic effect) as well as hydralazine and reserpine. Both of these latter agents still hold a prominent place in the clinical management of patients with hypertension. The placebo-controlled double-blind studies carried out in the Veterans Administration Cooperative Study on Antihypertensive Agents (*1*) indicated that hydralazine

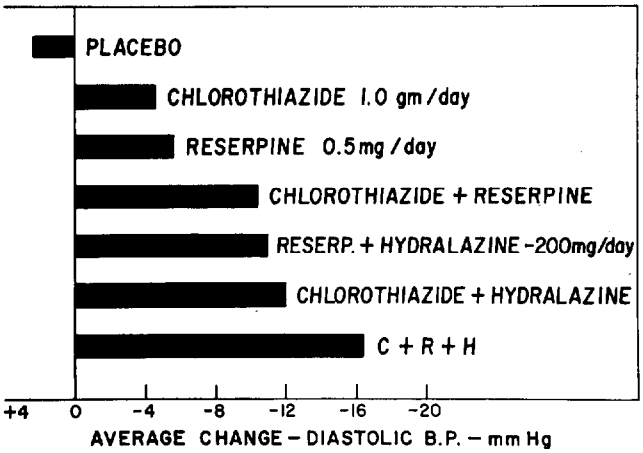

Figure 2. Results of Veterans Administration Cooperative Study on Antihypertensive Agents

Each bar represents average of large group of patients with mild and moderate hypertension, and refers to change in diastolic pressure from pretreatment hospital control values to 3 months posttreatment

and reserpine are most effective when combined with each other or with a saluretic agent.

Whereas there was a slight rise in the average diastolic blood pressure of the group of patients in the VA study receiving only placebos, there was a slight reduction in the groups receiving chlorothiazide alone or reserpine alone (Figure 2). In the patients who received chlorothiazide plus reserpine the reduction was approximately twice that obtained with either drug alone. Similar reductions in blood pressure were obtained with the combination of reserpine and hydralazine, or chlorothiazide and reserpine, while the administration of all three agents resulted in a highly significant blood pressure reduction.

Such results indicate that in the present state of development of antihypertensive drugs any new compound, which in itself may not be sufficiently potent to be relied upon for adequate blood pressure control, may still be clinically useful if its mode of action is different from previously known agents and it does not cause disturbing or dangerous side effects. Such new agents may be useful in combination with other drugs, as shown in the Veterans Administration Cooperative Study.

Conclusions

The most successful programs of molecular modification seem to have included recognition of clinical need and willingness to explore new approaches in answer to therapeutic problems. Among the antihypertensive agents, molecular modification of existing compounds has been most effective in the period immediately following the discovery of an agent with a new type of

action. Improvement beyond a certain point is prevented by inability to overcome clinically undesirable characteristics associated with the basic mode of action of a particular class of compounds. Early recognition of this point of diminishing returns should avoid unnecessary expenditure of time and effort.

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Discussion

C. J. CAVALLITO, presiding

Dr. John Holly (Ottawa): I would like to direct one question to Dr. Page. There is a general feeling, I know, among a number of clinicians, that women can tolerate an elevated blood pressure better than men. Does he believe this is statistically true, and why?

Dr. Page: I think the answer is probably yes, but not on a statistical basis. They do it on the basis that they cut a much better figure than we do as males. You have to face the fact that the battle of the sexes has long since been won by the female. She has a longer life span, she is a healthier person, and she is running things anyway.

So if you think it is a man's world, remember it is in your wife's name.

Dr. Louis Friedman (U. S. Vitamin): Is it due to hormonal differences?

Dr. Page: I suspect it is, but I have not the slightest idea which hormone. You see, there is supposed to be a difference between femininity and being a woman and this is a distinction which I hesitate to bring up with my wife.

Dr. Cavallito: I would like to ask Dr. Freis if it would be fair to conclude from his presentation that although in numerous instances molecular modification has not led to a significant improvement, yet there have been cases of definite improvement. Do you think this is a reasonable assessment of the past ten or fifteen years?

Dr. Freis: Yes. I tried to give some examples of that. The modification of SU-4029, which was not very successful clinically, led to guanethidine which was a most successful modification, whereas a great deal of work went into modifying thiazides and most of this has not led to any great practical advantage. The same could be said for the ganglionic blocking drugs after pentolinium tartrate had been developed.

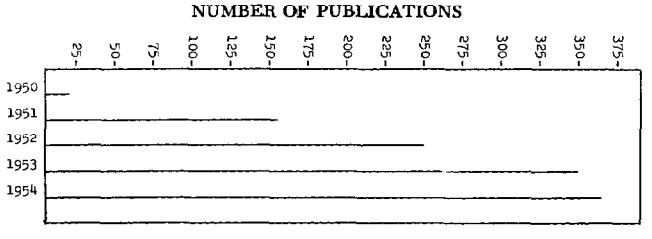
Dr. Cavallito: Would it also be fair to say that one would not know this in advance of implementing the molecular modifications?

Dr. Freis: I do not know about that. I would think one would have guessed after about the first 50 modifications of chlorothiazide and those that hit the market, that further modifications might not be of any great value. That could have been said of the benzothiadiazines, and of the ganglionic blocking agents.

There is a tendency to proceed on one line a little long in pharmaceutical research. This may be profitable; I do not know. But it is not scientifically or therapeutically very profitable. I think there is a time to quit.

Dr. Cavallito: I have one more question, and in leading up to it, I would like to show one illustration.

I recall that ten or fifteen years ago one of the questions was: Is it really useful to lower blood pressure? The consensus at that time seemed to be that you had better leave it alone. For a talk presented in mid-1955, I was interested in getting some reflection of the amount of interest in hypertension and its therapy, and plotted as a reflection of interest the number of publications that appeared per year, covering the chemistry, pharmacology, and clinical aspects of hypertension. Using the same general background of available literature, this chart shows clearly the rapid increase in interest in hypertension and its therapy as reflected by the literature.



I would like to ask Dr. Freis if he feels that therapy or treatment of hypertension is really useful, from the standpoint of the patient's well-being and ultimate life expectancy.

Dr. Freis: I think that it has been proved that in malignant hypertension you can prolong the lives of many patients and can salvage the lives of many more patients than you could before any hypertensive drug therapy, and that in the mild and moderate grades of hypertension, there is a great deal of circumstantial evidence to indicate that reduction of blood pressure should prolong

lives by decelerating, or slowing down, the process of degenerative vascular diseases. There is a lot of evidence to indicate that elevation of blood pressure is bad for blood vessels, accelerates atherosclerosis and arteriosclerosis, and promotes hypertrophy of the heart, and other bad things.

That being the case, one would expect reduction of blood pressure to be beneficial. It has been shown in experimental animals that animal atherosclerosis can go on at the same rate as in a normotensive animal if you make the animal hypertensive but keep his blood pressure from going up by giving him antihypertensive agents.

In man it is difficult to run a controlled trial. It takes many years to determine whether or not a patient with mild or moderate hypertension is going to develop organic complications. The only kind of studies we have are sort of hindsight studies which are not very valid, but even these suggest that in mild and moderate hypertension, life is prolonged by adequate blood pressure control.

Dr. Page: As Dr. Freis suggested, this is our life blood. It has got to work. The evidence to me is incontrovertible. The first bit that was mentioned by Dr. Freis, the reversal of malignant hypertension, has no question about it; nobody would question it today.

Believe me, in the first days, there was a pretty dismal group to take care of. All you could do was give better nursing, because the outlook was universally fatal.

The second thing to realize is that it is not the height of the blood pressure that really kills the individual. It is the effect of blood pressure and other factors on the smooth muscles of the body. If you plot any measurement which measures the change in the quality of smooth muscle, you will find that antihypertensive drugs do make the curve of deterioration level out.

The third thing—one that Dr. Freis did not mention—is that when there is heart failure, very often antihypertensive reduction of blood pressure will overcome the heart failure without even the use of digitalis.

So if you put all these things together, we need not really go into computer medicine or large scale statistics to prove what clinical experience and physiological thinking will show you really happens.

I would like to add just one more piece of advice—that I think the pharmaceutical industry and the chemists have perhaps restricted their thinking a little too much in the kinds of drugs that they have worked with, as Dr. Freis suggested. Perhaps they overdid the saluretic drugs and have not given enough attention to the many other facets of the problem of blood pressure control which are now apparent to anyone who works in the physiology and chemistry of mechanisms which control blood pressure.

Therefore you have got your work cut out for you, and you do not have to keep beating some of the horses that are fairly well dead in order to accomplish things. I would like to see another striking out anew and approaching some of these other mechanisms which are just crying to be antagonized or to be used in order to lower blood pressure.

Dr. Cavallito: In essence it is evident that the work of the past ten or fifteen years has not been in vain. However, it is also evident that you still have some unresolved problems.